Literature Report

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Article

Platinum-Triggered Bond-Cleavage of Pentynoyl Amide and *N*-Propargyl Handles for Drug-Activation

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Gonçalo J. L. Bernardes

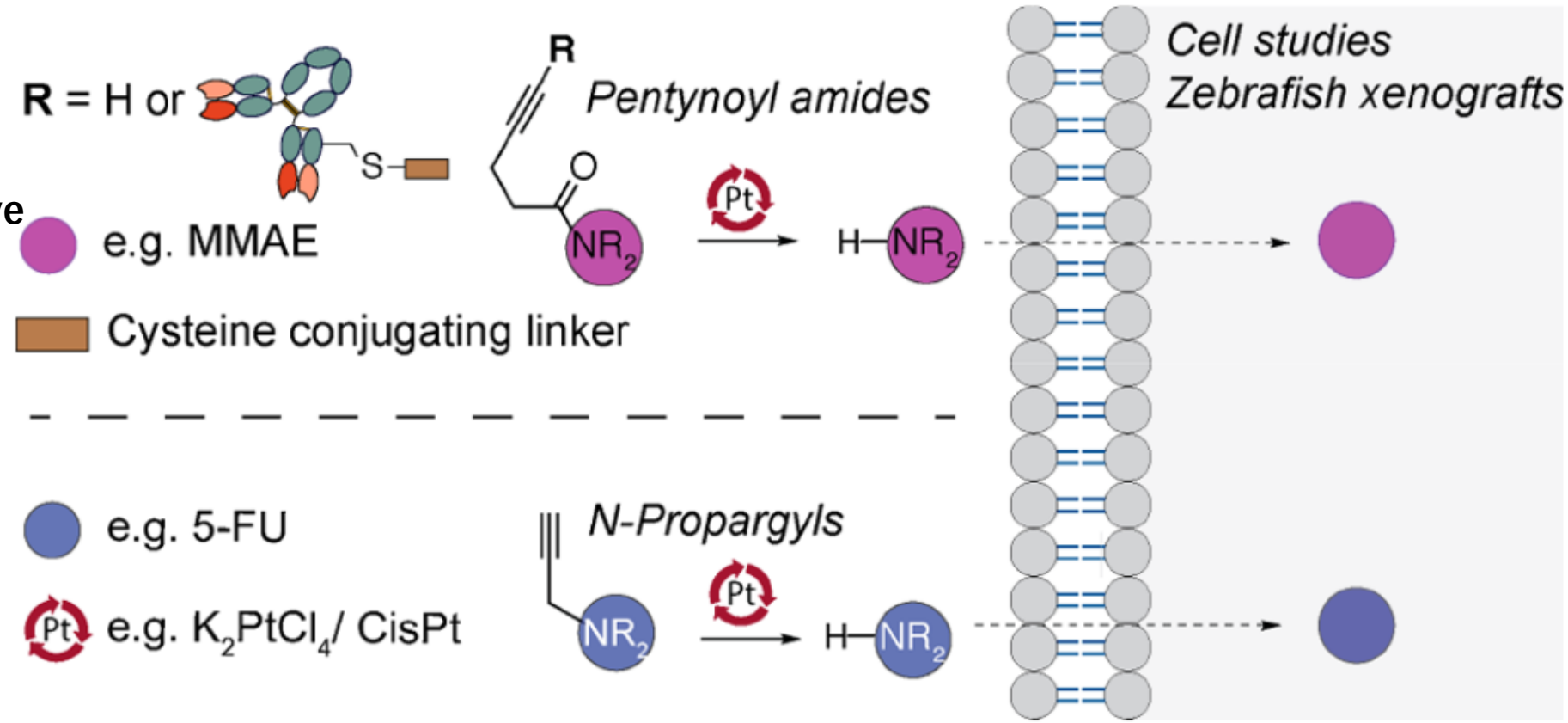
◇He graduated in Chemistry from the University of Lisbon in 2004 and soon moved to the University of Oxford where he completed his D.Phil.
◇At Oxford, he worked on reaction engineering for site-selective protein modification.
◇Gonçalo moved to the ETH Zürich to join the lab of Prof. Dario Neri. At ETH, and as an EMBO Fellow he developed novel vascular targeting antibody-drug conjugates (ADCs) for cancer therapy.
◇He started his independent research career in 2013 at the University of Cambridge as a Royal Society University Research Fellow. His research group interests focus on the use of chemistry principles to tackle challenging biological problems for understanding and fight cancer.

CisPt

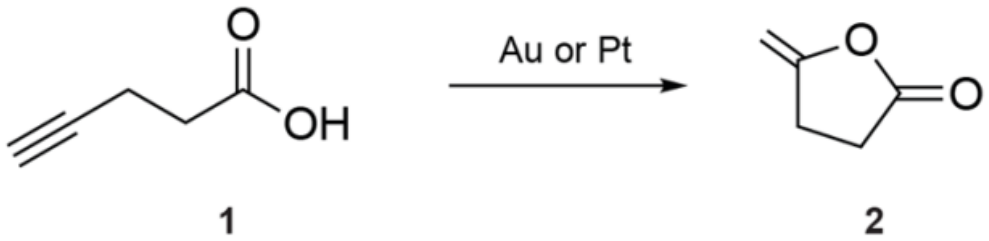
highly reactive

half-life

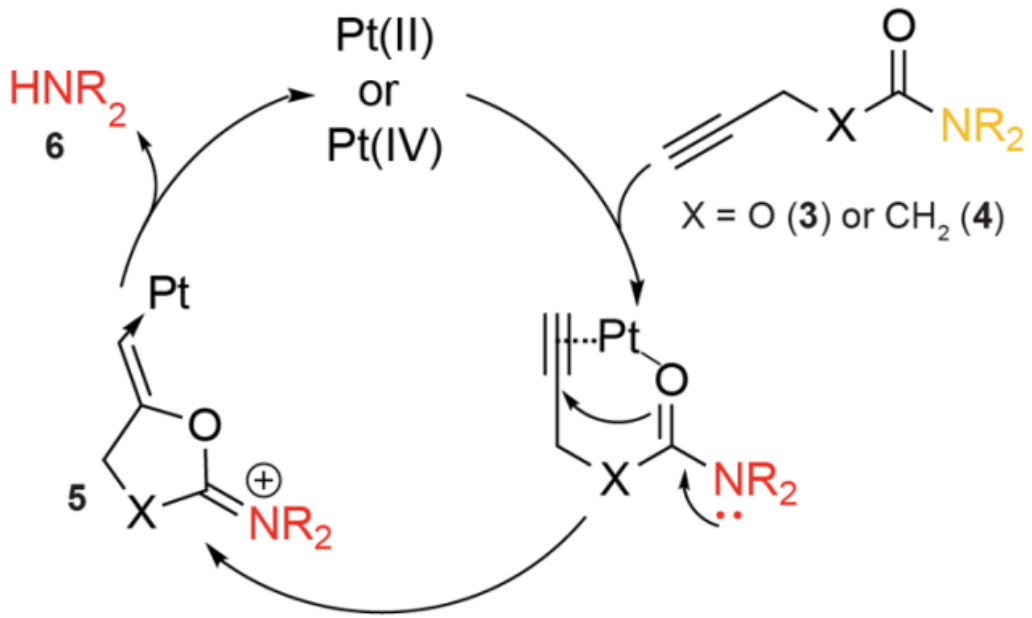
Scheme 1. Platinum-Mediated Bioorthogonal Bond Cleavage[a]



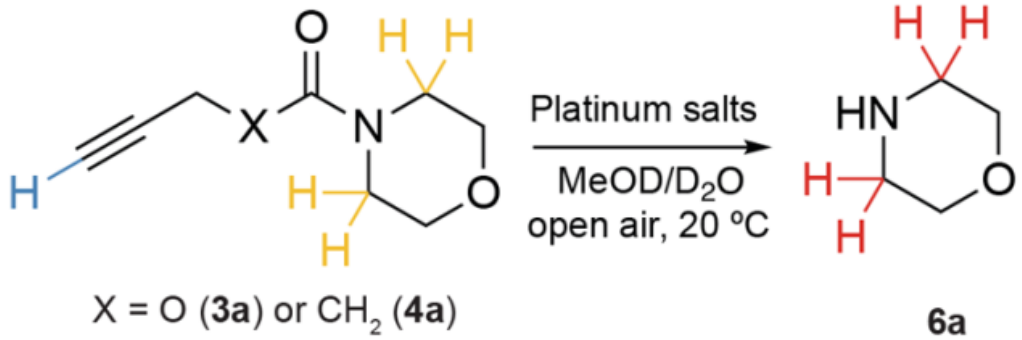
a Previous work



b This work



c Catalytic decaging of tertiary amides



X = O (**3a**) or CH_2 (**4a**)

6a

d Conversions

Entry	Metal	Equiv.	Compound	Conversion %[a]
1	K_2PtCl_4	0.1	3a	20 ± 6
2	K_2PtCl_4	2.0	3a	61 ± 1
3	K_2PtCl_4	0.1	4a	37 ± 1
4	K_2PtCl_4	2.0	4a	50 ± 1
5	K_2PtCl_6	0.1	4a	43 ± 3
6	K_2PtCl_6	2.0	4a	81 ± 7

[a] monitored by NMR

Figure 1. Platinum-mediated decaging reaction engineering.

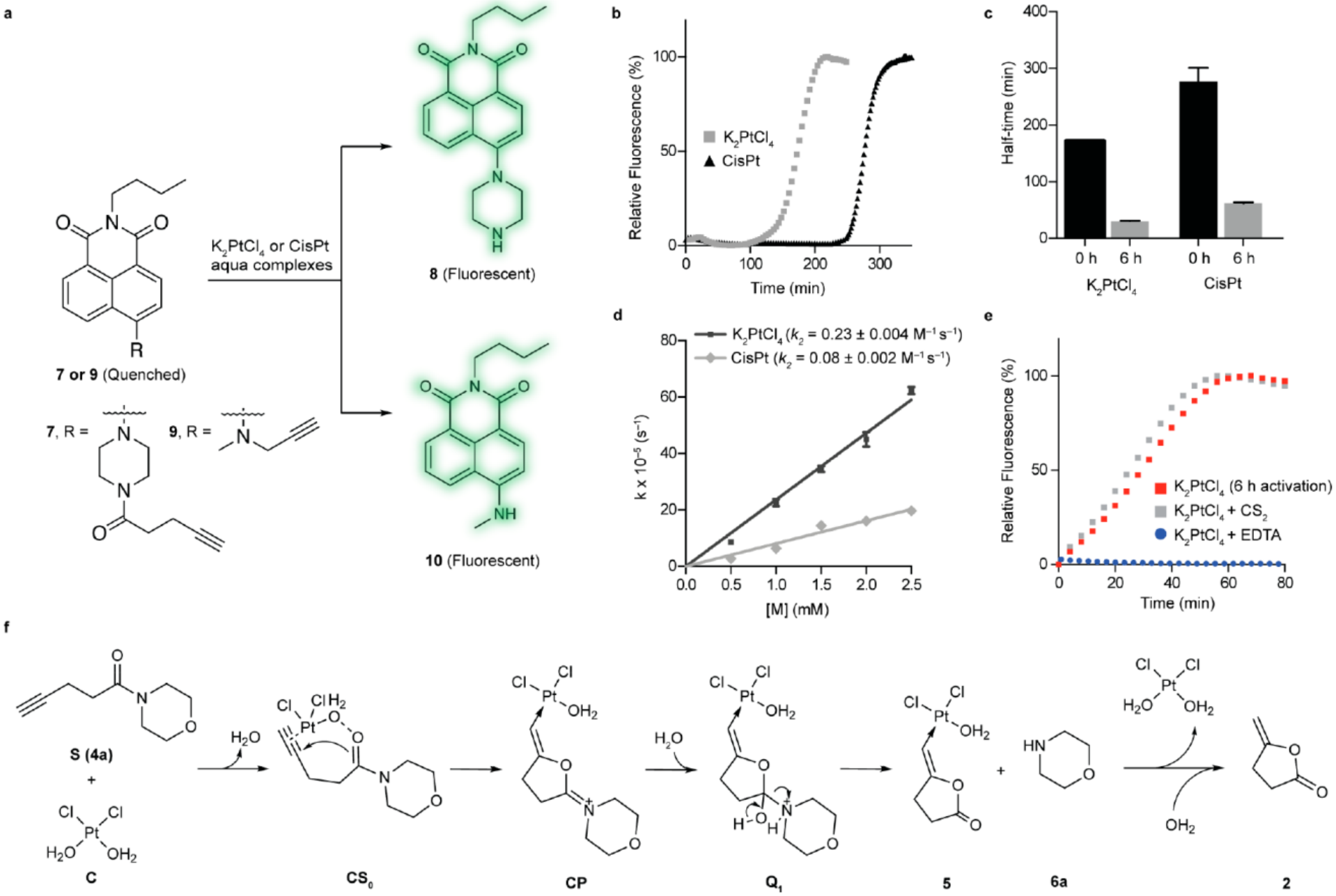


Figure 2. Examination of the platinum-catalyzed bioorthogonal cleavage reaction.

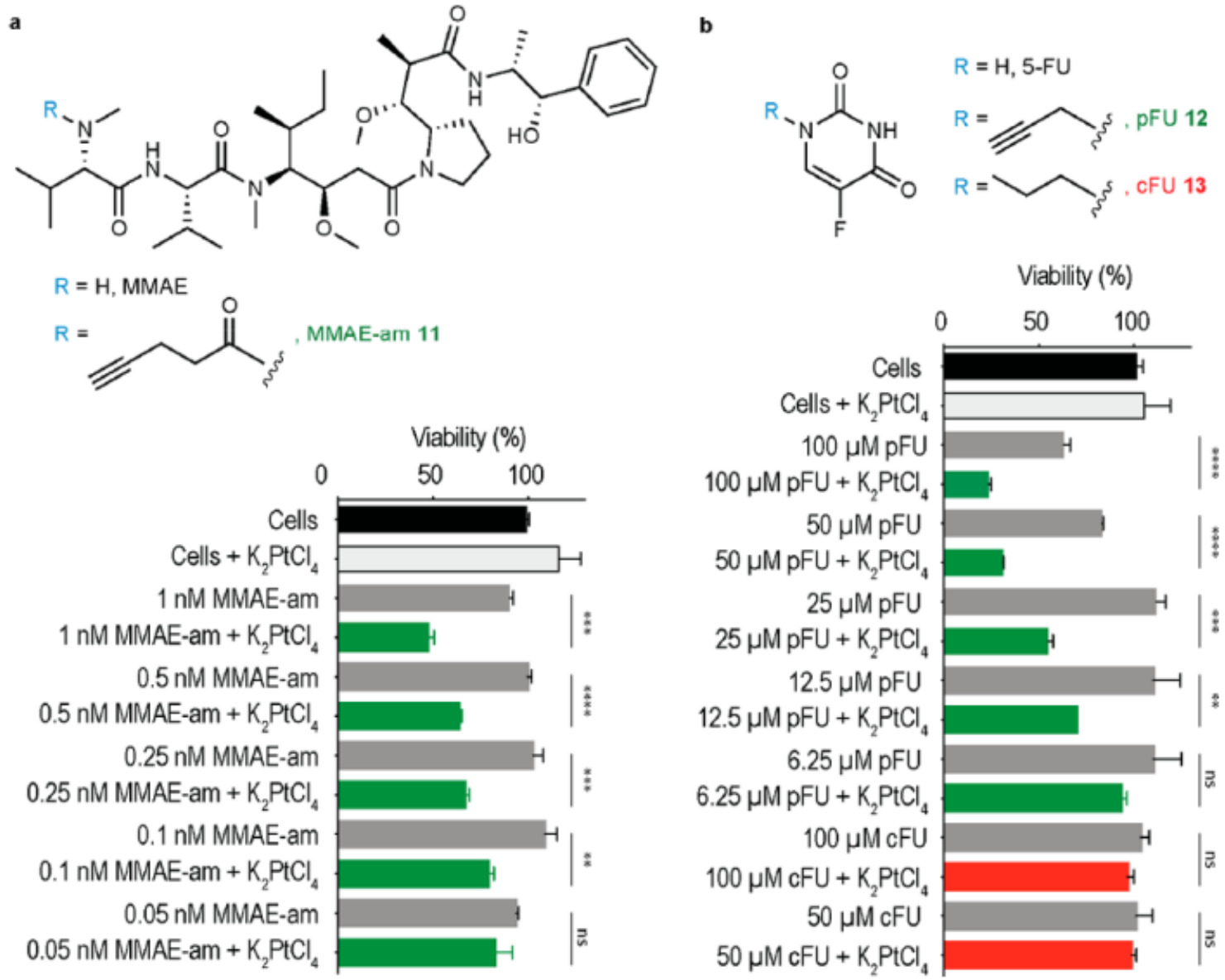
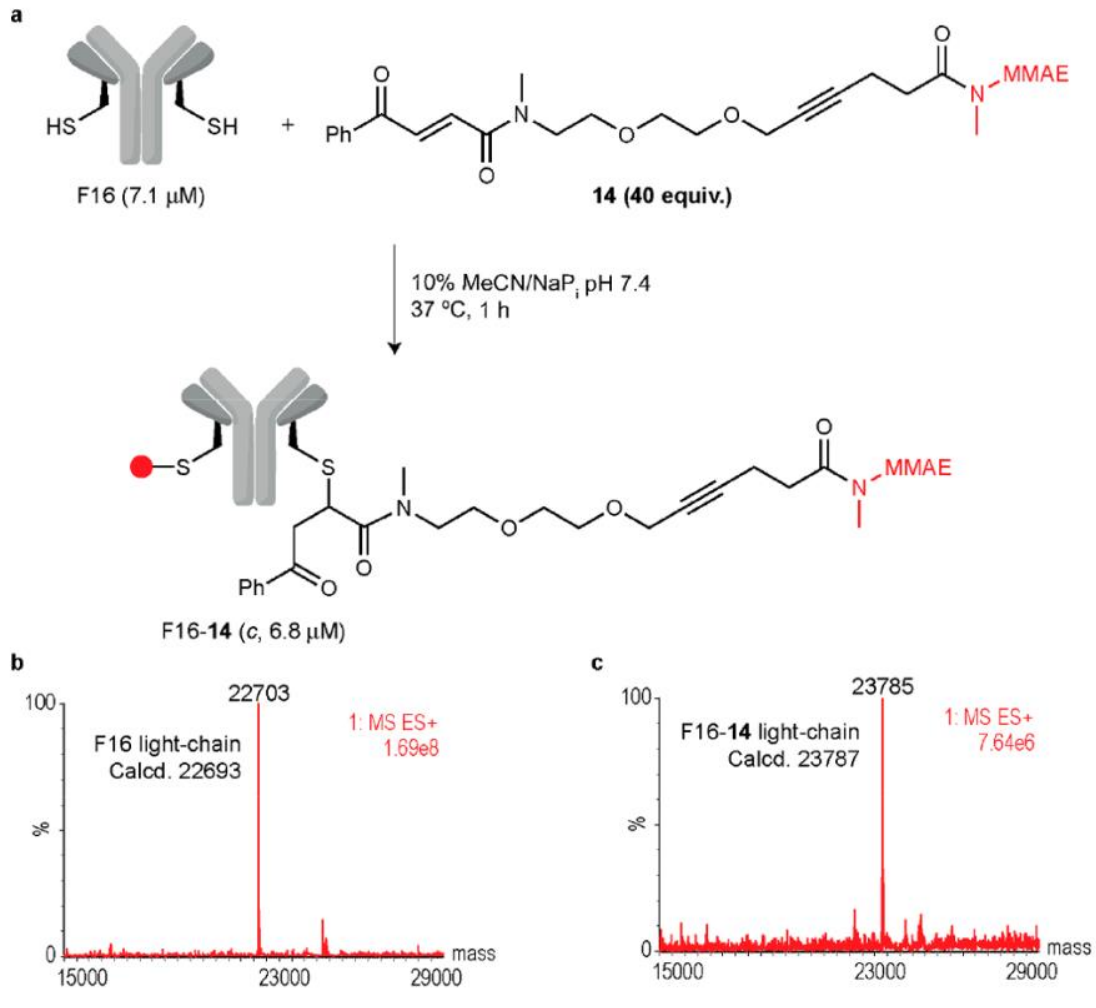


Figure 3. Platinum-mediated decaging in cells.



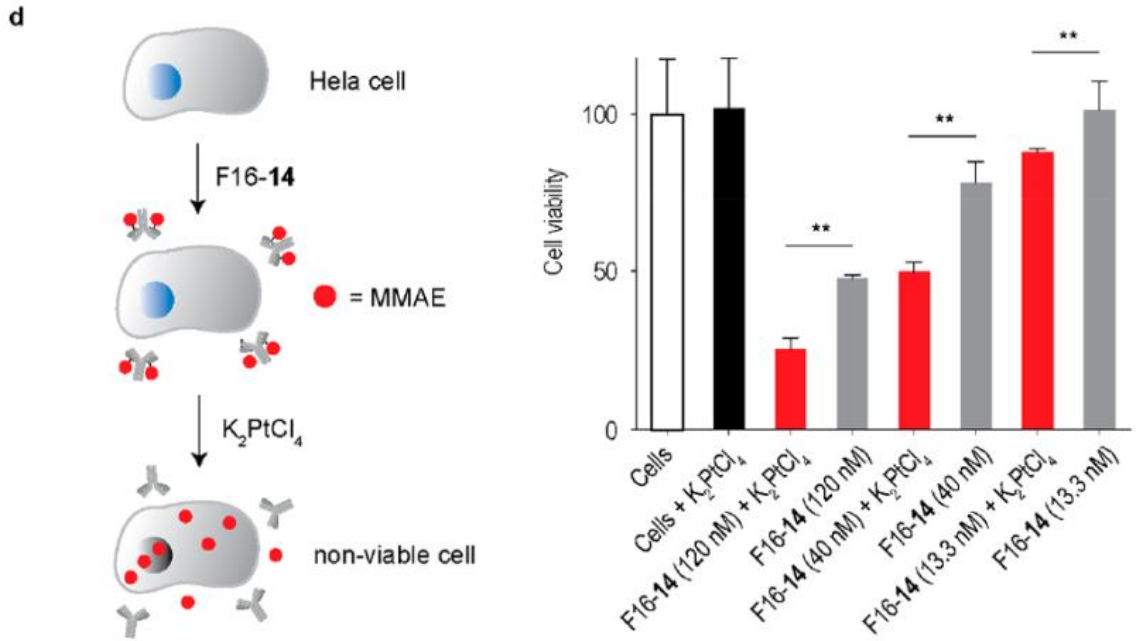


Figure 4. Platinum-mediated drug decaging from a noninternalizing ADC

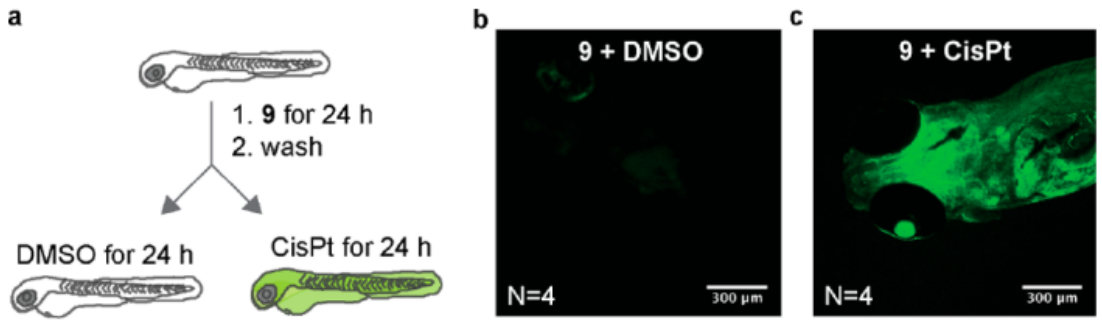
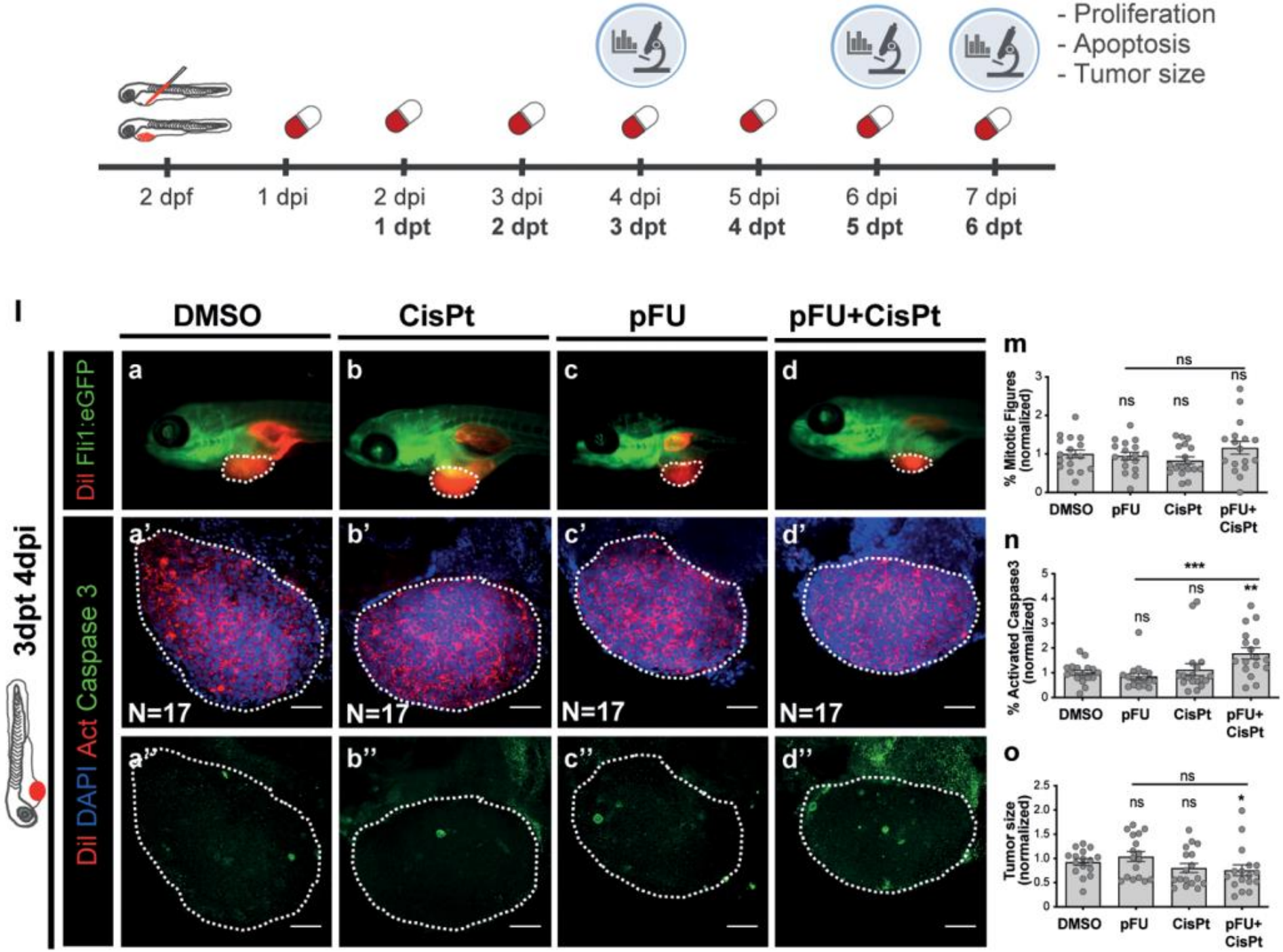


Figure 5. CisPt Decages the Fluorogenic Probe 9 in vivo.


- Proliferation
- Apoptosis
- Tumor size
2 dpf
1 dpi
2 dpi
1 dpt
3 dpi
2 dpt
4 dpi
3 dpt
5 dpi
4 dpt
6 dpi
5 dpt
7 dpi
6 dpt
l
DMSO
CisPt
pFU
pFU+CisPt
3dpt 4dpi
DiI Fli1:eGFP
DiI DAPI Act Caspase 3
a
b
c
d
a'
b'
c'
d'
a''
b''
c''
d''
N=17
m
% Mitotic Figures (normalized)
ns
DMSO
pFU
CisPt
pFU+ CisPt
n
% Activated Caspase3 (normalized)
***
**
o
Tumor size (normalized)
*

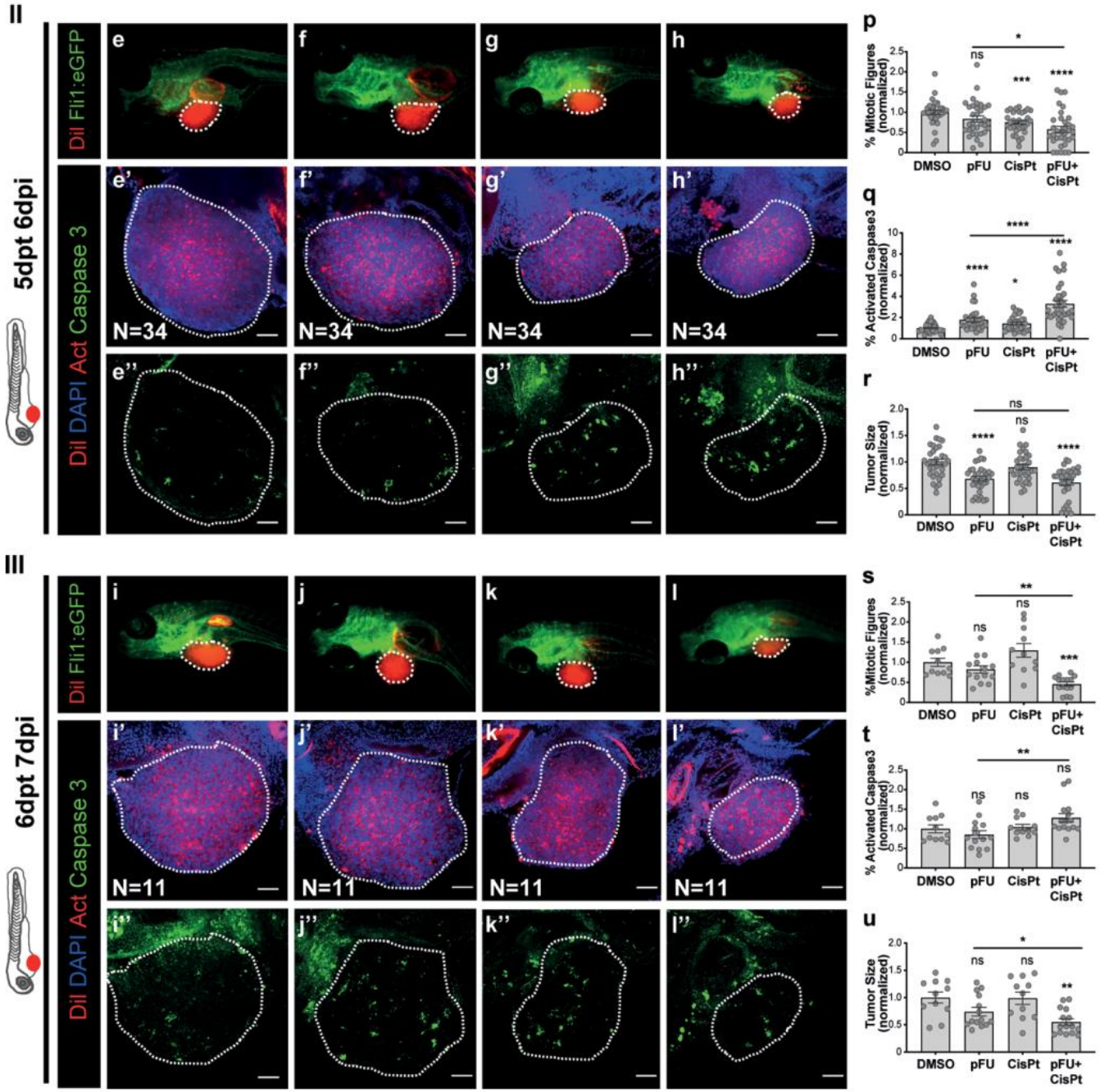


Figure 6. CisPt-mediated prodrug decaging in zebrafish xenografts

Thanks !